

Preliminary Study on Virtual MRI Generation Driven by 3D Intraoperative Ultrasound Deformation Field for Glioma Surgery

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Article

Keywords: brain shift, 3D intraoperative ultrasound, deformation field prediction, virtual MRI, optical navigation, glioma, non-rigid registration

Posted Date: August 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10276504/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on September 21st, 2026. See the published version at <https://doi.org/10.1038/s41598-026-71616-w>.

Preliminary Study on Virtual MRI Generation Driven by 3D Intraoperative Ultrasound Deformation Field for Glioma Surgery

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Abstract

Objective: Intraoperative brain shift impairs preoperative MRI-based navigation, while intraoperative MRI (iMRI) is costly. This study explored a deformation field prediction method using 3D intraoperative ultrasound (3D iUS) and optical navigation to generate virtual MRI (vMRI) via non-rigid registration, providing a low-cost, high-precision guidance scheme for glioma resection.

Methods: An optical-ultrasound navigation platform unified 3D iUS and preoperative MRI coordinates. In vitro brain shift phantoms and ex vivo cadaveric specimens simulated bidirectional tumor growth-resection deformation. A B-spline free-form deformation algorithm computed tissue displacement fields from 3D iUS to generate vMRI. Target registration error (TRE) between vMRI and iMRI was calculated using implanted markers and anatomical landmarks. Algorithm performance was assessed by accuracy, real-time capability, and robustness.

Results: After deformation correction, mean TRE was 2.94 mm in vitro and 2.28 mm ex vivo, both within the clinically acceptable range (2–3 mm). Image overlay confirmed good alignment of key structures. The algorithm ran stably with a mean single-registration time of approximately 2.5 minutes, demonstrating acceptable near-real-time performance.

Conclusion: The "3D iUS + optical navigation + deformation field" pipeline is feasible in vitro and ex vivo, achieving clinically acceptable

registration accuracy. These findings provide a methodological foundation for future in vivo validation and iMRI-free dynamic image-guided navigation.

Keywords

brain shift; 3D intraoperative ultrasound; deformation field prediction; virtual MRI; optical navigation; glioma; non-rigid registration

Abbreviations

3D iUS: three-dimensional intraoperative ultrasound; iMRI: intraoperative magnetic resonance imaging; vMRI: virtual magnetic resonance imaging; TRE: target registration error; B-spline: basis spline; DTI: diffusion tensor imaging; LGG: low-grade glioma; CEUS: contrast-enhanced ultrasound; SWE: shear wave elastography; SMI: superb microvascular imaging

1. Introduction

With the aging of the global population accelerating, the incidence and mortality of malignant tumors keep rising, evolving into a major worldwide public health burden^[1]. Glioma ranks among the most prevalent primary malignant tumors of the central nervous system, accounting for around 30% of all intracranial neoplasms and 80% of malignant brain lesions^[2]. According to the GLOBOCAN 2022 database, there were approximately 321,624 new cases of brain and central nervous system cancers worldwide in 2022, with an age-standardized incidence rate of 3.5 per 100,000 people^[3]. Characterized by infiltrative invasive growth, gliomas have ill-defined boundaries with normal brain parenchyma, leading to high postoperative recurrence and poor overall prognosis; the 5-year survival rate of glioblastoma remains only 5%^[4]. At present, surgical resection serves as the primary therapeutic strategy for glioma, whose core goal is maximal lesion removal while preserving adjacent neurological functions^[5]. Therefore, real-time and precise intraoperative identification of tumor margins and eloquent brain regions is decisive for surgical outcomes and long-term patient survival.

Nevertheless, accurate maximal safe resection is largely hampered by intraoperative brain shift. After craniotomy decompression, cerebrospinal fluid loss, tumor debulking, gravity traction and mechanical stretch induce unpredictable non-rigid brain tissue displacement, which occurs in up to

66% of surgical cases^[6, 7]. This generates obvious anatomical mismatch between static preoperative MRI and real-time intraoperative fields, resulting in navigation failure. Such delayed imaging information may cause tumor residual and elevated recurrence risk; aggressive resection to eliminate lesions may also injure vital functional areas and trigger permanent neurological deficits. A 2025 clinical study reported by Rai et al. further verified the severity of brain shift: significant tissue displacement appeared right after dural opening and aggravated after tumor resection, shifting diffusion tensor imaging (DTI)-derived corticospinal tracts from resection cavity edges to the cavity center^[8]. Without timely image correction, surgeons would be seriously misled and face higher functional injury risks. Hence, intraoperative imaging tools capable of real-time anatomical localization and tissue deformation tracking are urgently required to improve resection precision, optimize patient prognosis and rationalize medical resource allocation.

Intraoperative magnetic resonance imaging (iMRI) and intraoperative ultrasound (iUS) are two mainstream modalities to counteract brain shift. iMRI delivers high-resolution, high-contrast three-dimensional images and is regarded as the gold standard for brain shift compensation^[9, 10]. However, its exorbitant price, long scanning duration, strict MR-compatible operating room requirements and magnetic field limits on surgical instruments restrict large-scale clinical promotion^[11]. In contrast, iUS

offers real-time imaging, easy operation, zero ionizing radiation and low cost^[12]. It clearly visualizes tumor borders, cerebral sulci and gyri, ventricular walls, falx cerebri based on tissue acoustic impedance differences^[13]. Conventional B-mode ultrasound suffers from lower spatial and soft-tissue contrast than MRI, and is susceptible to noise and imaging artifacts; its interpretation heavily relies on surgeons' clinical experience^[14].

Clinically, preoperative MRI–iUS fusion navigation is widely adopted to complement the strengths of two imaging modalities, making multimodal registration a hot research direction^[15-17]. However, huge disparities in imaging mechanisms and visual features make it difficult for clinicians to build intuitive anatomical correspondence between two modalities. Simple rigid spatial overlay cannot offset intraoperative non-linear brain deformation. Once brain shift distorts ultrasound images, the navigation system fails to dynamically update preoperative MRI, leading to inaccurate fused images. Therefore, developing a method that dynamically and non-rigidly revises preoperative MRI based on real-time iUS data has become the core bottleneck to break through current technical limitations.

Several research groups attempted elastic fusion between intraoperative CT (iCT) and preoperative MRI to synthesize virtual MRI without iMRI devices, yet this strategy has inherent drawbacks. iCT shows

low sensitivity to tiny residual tumors and nearly half of small lesions may be overlooked; repeated intraoperative CT scans expose patients to ionizing radiation. In addition, CT lacks sufficient soft-tissue contrast to identify non-enhanced low-grade gliomas (LGG) ^[18]. Compared with iCT, 3D iUS realizes radiation-free, repeatable real-time scanning and clearly displays ventricles and cerebral sulci, acting as a superior data source for intraoperative deformation estimation and high-fidelity vMRI generation.

Against this clinical background, this study systematically designed and validated a novel technical pipeline built on an in-house high-precision optical-ultrasound navigation platform. Intraoperative three-dimensional ultrasound time-series data were processed via a deformation field solver to calculate non-rigid brain displacement, which warps preoperative MRI to produce dynamic virtual MRI matching real-time anatomical conditions. A stepwise verification workflow from in vitro phantoms to intact cadaver specimens was adopted to verify pipeline feasibility and lay a methodological foundation for subsequent in vivo clinical trials.

2. Materials and Methods

2.1 Experimental Platform and Data Acquisition

2.1.1 Construction of Optical-Ultrasound Navigation System

An optical positioning ultrasound navigation platform was established to integrate iUS and preoperative MRI into a unified coordinate system,

involving four core coordinate frames (Fig. 1): world coordinate system (W) defined by Polaris Vicra optical tracker, ultrasound probe tracker coordinate system (M), three-dimensional ultrasound image coordinate system (I), preoperative 3D MRI voxel coordinate system (R). Coordinate transformation included three core steps:

1. Ultrasound probe calibration: The N-wire phantom method was adopted to solve the transformation matrix ($T_M \leftarrow I$) between ultrasound image coordinates and probe coordinates, establishing spatial matching between imaging planes and the transducer.

2. Patient rigid registration: Scalp fiducials were used to calculate transformation ($T_W \leftarrow R$) linking the world frame to MRI coordinates to realize rigid alignment between preoperative images and specimen anatomy.

3. Real-time optical tracking: The optical camera continuously captured the dynamic transformation matrix ($T_W \leftarrow M$) from the probe to the world coordinates.

Combined coordinate mapping formula:

$$P_R = T_W \leftarrow R^{-1} \times T_W \leftarrow M \times T_M \leftarrow I \times P_I \quad (1)$$

Although rigid registration cannot compensate brain tissue deformation, it provided stable initial spatial alignment for subsequent deformation field calculation.

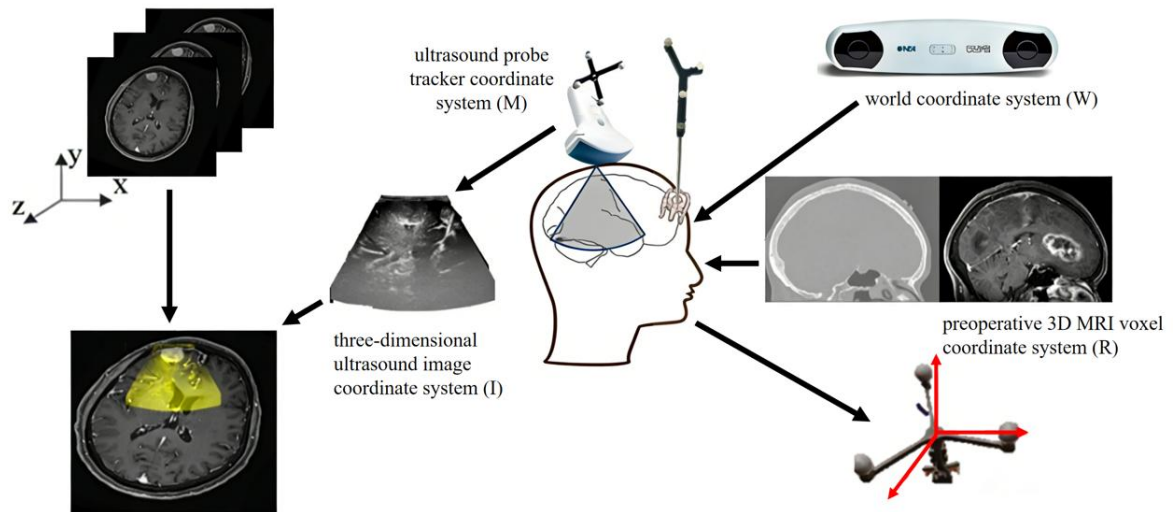


Fig.1 Definition of coordinate systems and transformation matrices of the optical-ultrasound navigation system

2.1.2 Multimodal Imaging Protocols

All multimodal images were collected under unified standardized scanning workflows.

Preoperative MRI: GE Discovery MRI 750 scanner; 3D T1 BRAVO (TR/TE = 8.2/3.2 ms, slice thickness = 1 mm), 3D T2 CUBE (TR/TE = 2500/Maximum ms, slice thickness = 1 mm).

Preoperative CT: GE Revolution Apex CT scanner, slice thickness = 1 mm, used to extract skull surface markers for spatial registration.

Intraoperative 3D ultrasound: Sonoscape SU11A EXP ultrasound system equipped with VC6-2 3D volume probe (central frequency 3.5–5.5 MHz, imaging depth 5–12 cm). Images were acquired under B-mode,

mechanical index controlled below 1.0, raw data exported in DICOM format.

2.2 Brain Shift Simulation Models

2.2.1 In Vitro Carrageenan Brain Phantom

Carrageenan gel was selected for phantom fabrication due to favorable elasticity, homogeneous imaging appearance and simple preparation, suitable for preliminary methodological validation.

Tumor simulant: A balloon filled with 50 mL normal saline was used to simulate tumor mass effect. The balloon wall presented arc-shaped hyperechoes on ultrasound and hyperintense signals on T2WI MRI, enabling cross-modal identification.

Multimodal tracking markers: Superabsorbent polymer microspheres served as fiducials. After hydration, particles displayed round anechoic regions on ultrasound and hyperintense signals on MRI T2WI with stable multimodal visibility. Markers were implanted in four layers with ≥ 20 beads per layer (over 40 total) to achieve dense three-dimensional deformation sampling.

The deformation device consisted of an outer transparent acrylic container, internal fixing fixtures and volume control syringe. The 15 cm cubic container had a fully open top for ultrasound scanning, with seven tracking fiducials pasted on the outer wall. The balloon and markers were

placed in the upper middle area of the container, connected to an injection syringe via heat-sealed catheter. Stepwise saline injection simulated tumor expansion and surrounding tissue compression; sequential fluid withdrawal replicated tissue collapse after tumor resection.

2.2.2 Formalin-Fixed Human Cranial Cadaver Model

This study was performed on formalin-fixed adult human cranial specimens, all of which were sourced from the body donation program of Sun Yat-sen University. All donors voluntarily donated their bodies for scientific research and educational purposes. The entire study was conducted in strict accordance with the Declaration of Helsinki (revised in 2013). Written informed consents were obtained from all donors and their family members. All experimental procedures complied with national and institutional guidelines regarding body donation, as well as Articles 1, 3 and 5 of the Administrative Measures of Guangzhou Municipality on Voluntary Body Donation. The Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University waived the requirement for full ethical review, as all individuals had voluntarily donated their bodies for scientific research. Investigators only had access to the basic demographic information of the donors, including age and gender, and no other private personal data was available.

Specimen inclusion criteria: intact skull, clear midline anatomical structures (ventricles, falx cerebri), intact cerebral sulcal morphology, no

intracranial lesions or trauma history. A 5 cm × 5 cm temporoparietal craniotomy was created. Under ultrasound guidance, an empty balloon was implanted into periventricular brain parenchyma, with the catheter routed out through the bone window and fixed. Five CT/MRI-compatible markers were attached to the skull surface, and optical probe landmark sampling was performed for spatial registration. Lateral ventricular margins, falx cerebri attachment points and cerebral sulcus intersections were selected as tracking landmarks. These structures exhibited distinct hyperechoes on ultrasound and definite anatomical boundaries on MRI, and could be continuously tracked across all deformation states^[19]. Deep nuclei and acoustically unstable vascular structures were excluded to guarantee robust landmark tracking.

2.3 Virtual MRI Generation Pipeline

Virtual MRI synthesis contained three core steps:

1. Offline co-registration of baseline preoperative 3D MRI and 3D ultrasound before surgery to build static spatial reference frame.
2. Intraoperative 3D ultrasound acquisition followed by non-rigid registration to calculate full-volume tissue deformation fields.
3. Warping of preoperative MRI via solved deformation fields and image resampling to generate real-time intraoperative vMRI.

A B-spline free-form deformation model was adopted as the core registration algorithm. Compared with biomechanical and deep learning-

based models, B-spline achieved a balanced trade-off among registration accuracy, computational cost and interpretability. Grid control points captured local brain tissue deformation while global smoothness constraints guaranteed continuous displacement fields. Adaptive parameter tuning was implemented for different experimental scenarios (Fig.2): high-density grids for in vitro phantoms to maximize registration precision, sparse grids for cadaver specimens to accelerate computation; advanced normalized cross-correlation was selected as similarity metric to counter ultrasound gain artifacts; multi-resolution pyramid coarse-to-fine optimization combined with random coordinate sampling was adopted to shorten calculation time; mask segmentation was utilized to exclude skull and air interference during registration.

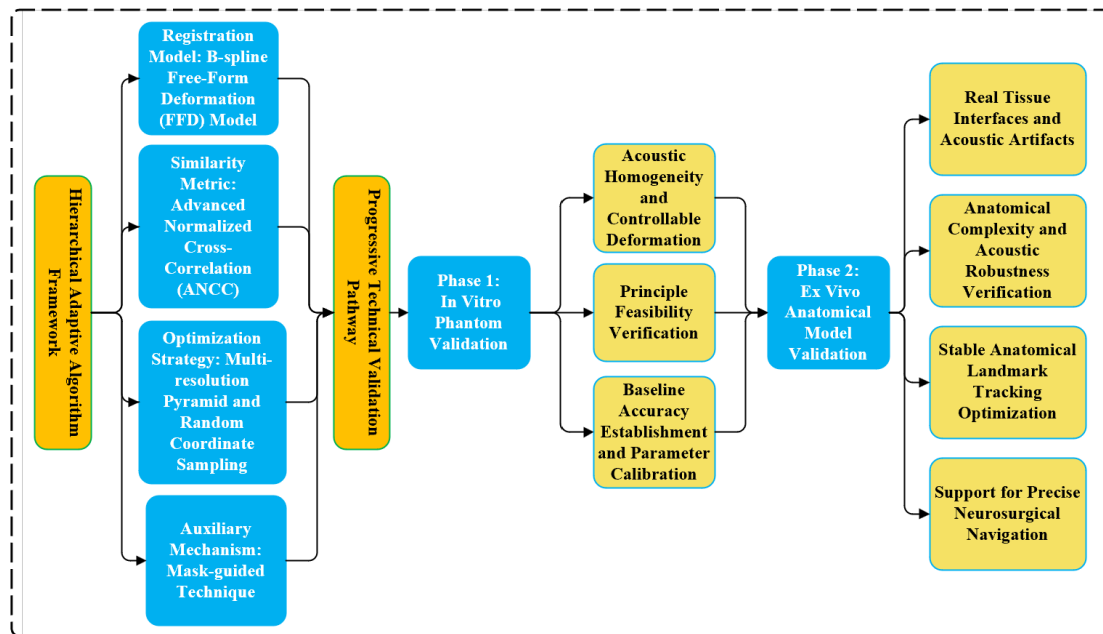


Fig.2 Schematic diagram of scene-adaptive deformation field solving strategy

2.4 Experimental Design and Quantitative Evaluation

2.4.1 In Vitro Phantom Experimental Protocol

Seven sequential deformation states (S0–S6) were designed to simulate bidirectional tissue shift processes. The balloon volume was incrementally increased from 50 mL to 80 mL (S0–S3) to simulate tumor growth, then decreased to 20 mL (S4–S6) to simulate resection decompression. After each volume adjustment, the phantom rested for 2 min to stabilize deformation, followed by ultrasound coordinate re-registration before data collection.

2.4.2 Cadaver Specimen Experimental Protocol

Seven deformation states (S0–S6) were also designed for cranial cadaver specimens. The balloon volume was adjusted from 5 mL to 25 mL (S0–S4) and then returned to 0 mL (S5–S6). Synchronous 3D ultrasound, MRI and navigation coordinate data were captured under each deformation phase.

2.4.3 Evaluation Metrics and Statistical Analysis

All ultrasound and MRI images were independently annotated by a physician with three years of cranial ultrasound experience using 3D-Slicer software. Coronal, sagittal and transverse multi-plane cross-location was adopted to guarantee consistent spatial coordinates of cross-modal landmarks.

Target Registration Error (TRE) was defined as the 3D Euclidean distance between each pair of matched anatomical landmark points. The calculation formula for TRE is shown in Equation:

$$TRE_i = \| \mathbf{p}_i^A - \mathbf{p}_i^B \|_2 = \sqrt{(x_i^A - x_i^B)^2 + (y_i^A - y_i^B)^2 + (z_i^A - z_i^B)^2} \quad (2)$$

where $\mathbf{p}_i^A$ and $\mathbf{p}_i^B$ represent the three-dimensional coordinates of the i-th landmark in image A and image B, respectively. The clinically acceptable TRE threshold for neurosurgical navigation was set as 2–3 mm^[7, 20-22]. Three evaluation dimensions were defined: (1) Initial rigid TRE (MRI vs US); (2) Cross-modal TRE (vMRI vs US); (3) Gold-standard TRE (vMRI vs intraoperative MRI). Algorithm performance was assessed from single registration runtime and operational stability.

Statistical analysis was performed with SPSS 27.0. Measurement data were expressed as mean $\pm$ standard deviation (mean $\pm$ SD). $p < 0.05$ represented statistically significant difference. Normality was tested via Shapiro-Wilk test; paired t-test was used for normally distributed TRE data, while Wilcoxon signed-rank test was adopted for non-normal data, with Cohen's d calculated as effect size.

3. Results

3.1 In Vitro Phantom Experimental Results

Initial rigid registration between preoperative MRI and baseline ultrasound yielded an overall mean TRE of 2.56 ± 0.88 mm, meeting the clinical 2–3 mm standard. Inter-group error fluctuations (2.05–3.27 mm)

originated from phantom repositioning and manual registration noise, with individual landmarks approaching 4 mm, which demonstrated inherent limitations of simple rigid alignment for non-linear brain deformation.

Cross-modal TRE between generated vMRI and intraoperative ultrasound averaged 2.99 ± 1.22 mm, 0.43 mm higher than rigid baseline, with $p > 0.05$ and Cohen's $d < 0.2$, indicating minor accuracy loss caused by multimodal mismatch.

Gold-standard TRE between vMRI and intraoperative MRI reached an overall mean of 2.94 ± 1.31 mm (Table 1), within clinical tolerance. Compared with rigid baseline (+0.38 mm) and cross-modal error (+0.05 mm), no significant statistical differences were observed ($p > 0.05$, Cohen's $d < 0.2$). State S3 exhibited maximal mean TRE of 4.10 mm, attributed to extreme tissue displacement amplitude.

Bar charts demonstrated consistent TRE distributions across three registration groups (Fig.3a). Image overlay showed severe anatomical misalignment between uncorrected preoperative MRI and intraoperative ultrasound, while deformation-warped vMRI perfectly matched balloon boundaries and implanted fiducials on ground-truth MRI (Fig.3b). Computational performance: Single registration consumed approximately 2.4 min (124 s deformation solving + 21 s image resampling), with stable execution across all deformation cycles without registration failure.

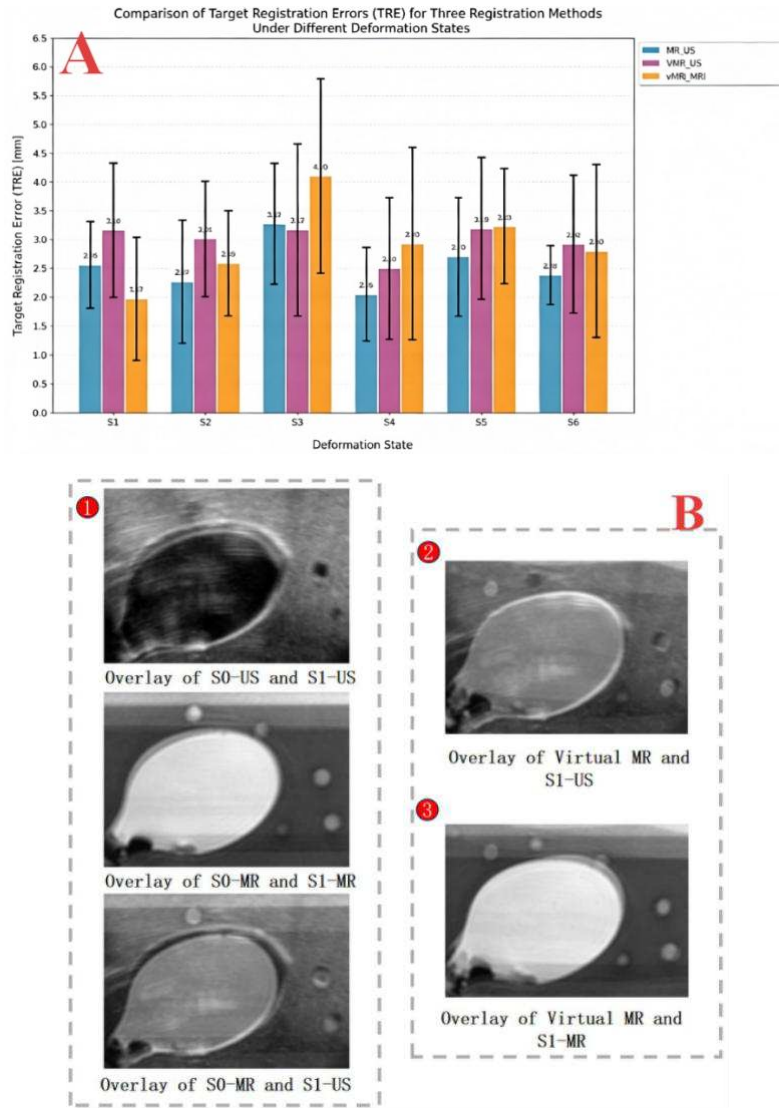


Fig. 3 In vitro experimental results. (A) Bar chart of three TRE metrics for all in vitro deformation states. (B) Multimodal overlay comparison of uncorrected and deformation-corrected in vitro phantom images

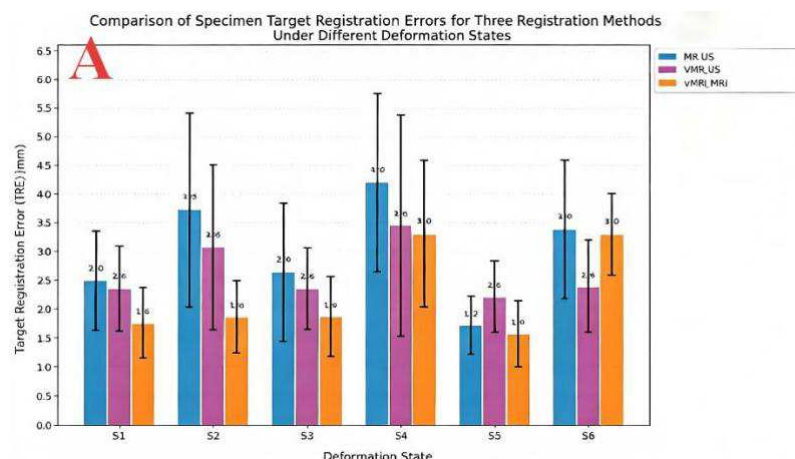
3.2 Cadaver Specimen Experimental Results

The overall mean initial rigid TRE (MRI vs US) for cadaver models was 2.84 ± 1.08 mm, meeting clinical standards. Group MRI4_US4 presented the maximum mean TRE of 4.20 mm with individual landmarks up to 6.46 mm, verifying the drawbacks of rigid registration under extensive anatomical shift.

Cross-modal TRE (vMRI vs US) averaged 2.64 ± 1.04 mm, 0.20 mm lower than rigid baseline ($p > 0.05$). High-baseline state S2 (3.73 mm) was reduced to 3.08 mm after non-rigid fusion, showing the smoothing effect of deformation correction.

Gold-standard TRE (vMRI vs intraoperative MRI) averaged 2.28 ± 0.75 mm (Table 1), 0.56 mm and 0.36 mm lower than rigid and cross-modal errors respectively ($p > 0.05$). Deformation correction introduced no extra spatial bias and maintained accurate anatomical restoration.

Bar plots (Figure 11) illustrated that gold-standard vMRI TRE remained lower or equivalent to rigid alignment across all states (Fig.4a). Overlay images visually validated precise matching of critical anatomical boundaries after deformation correction (Fig.4b). Algorithm performance: Average single registration runtime reached approximately 2.5 min; the deformation field maintained spatial continuity under acoustic shadow and multiple reflection ultrasound artifacts.



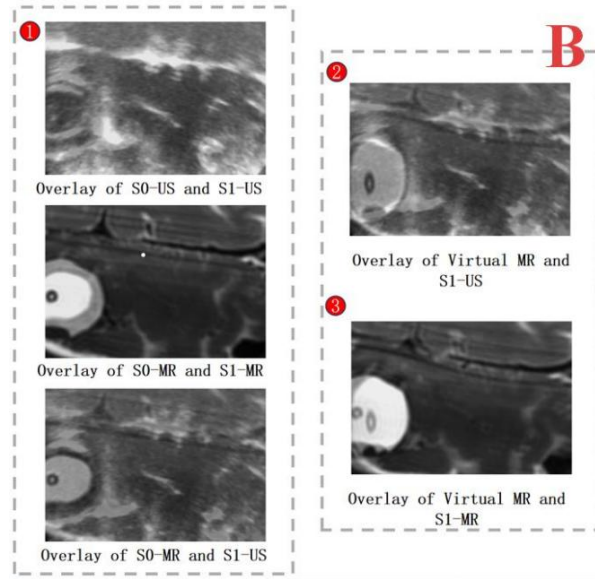


Fig.4 Ex vivo experimental results. (A) TRE bar chart for three registration metrics across cadaver deformation states. (B) Multimodal overlay comparison of raw and corrected cadaver specimen images

Table 1. Summary of target registration errors before and after deformation correction

Model	Registration Group	Mean TRE (mm)	SD (mm)
In vitro	Initial rigid (MRI vs US)	2.56	0.88
In vitro	Cross-modal (vMRI vs US)	2.99	1.22
In vitro	Gold-standard (vMRI vs MRI)	2.94	1.31
Ex vivo	Initial rigid (MRI vs US)	2.84	1.08
Ex vivo	Cross-modal (vMRI vs US)	2.64	1.04
Ex vivo	Gold-standard (vMRI vs MRI)	2.28	0.75

4. Discussion

This study validated the full pipeline of ultrasound-derived deformation field calculation and virtual MRI generation via both in vitro phantom and human cadaver models. In phantom experiments, rigid baseline TRE averaged 2.56 mm, with corrected gold-standard TRE of 2.94 mm ($p > 0.05$). Moderate deformation (S1) yielded 23.05% accuracy gain, while massive tissue shift (S3) induced error elevation. Cross-modal

TRE showed no statistical difference from gold-standard results. Cadaver experiments demonstrated baseline rigid TRE of 2.84 mm, reduced to 2.28 mm after correction (19.7% error reduction). The algorithm achieved far better compensation for progressive compressive deformation than post-resection tissue rebound. Visual multimodal overlays confirmed favorable anatomical alignment after non-rigid warping.

4.1 Feasibility of 3D Ultrasound as Deformation Sensing

Source

Stable multimodal visualization of fiducials and simulated tumor borders in phantoms verified that 3D iUS can reliably quantify tissue displacement. Nevertheless, ultrasound imaging quality is restricted by beam incident angle, acoustic attenuation and interface reflection, generating acoustic shadow artifacts behind target structures; intraoperative reverberation and side lobe noise further degrade signal quality. Multi-angle scanning and objective image quality evaluation metrics will be integrated in follow-up research to reduce bias in deformation solving. For cadaver specimens, high-echo structures such as ventricular walls and falx cerebri maintain stable acoustic interfaces during tissue shift, serving as robust continuous tracking landmarks consistent with clinical intraoperative navigation references.

4.2 Cross-Modal Registration Accuracy Analysis

Three layers of TRE comprehensively evaluated pipeline performance: rigid baseline TRE reflected inherent navigation platform precision; cross-modal TRE represented real-time intraoperative fusion visualization accuracy; gold-standard TRE quantified the efficacy of deformation field compensation. vMRI–iMRI TRE values were statistically comparable to rigid baseline across all deformation states, and cross-modal error showed negligible deviation from gold-standard results with small effect sizes, which proves that intrinsic ultrasound-MRI imaging discrepancies exert limited impact on registration precision. State-wise comparison revealed insufficient compensation capacity under extreme tissue displacement amplitudes.

4.3 Algorithm Robustness and Computational Latency

The registration pipeline tolerates moderate acoustic heterogeneity in tissue. State S4 with maximal mass effect and severe acoustic attenuation achieved corrected TRE of 3.32 ± 1.27 mm, significantly lower than rigid baseline (4.20 ± 1.56 mm), confirming that B-spline global smooth constraints partially counteract local ultrasound noise artifacts. Mean single registration time (~ 2.5 min) is drastically shorter than the reported average iMRI scanning duration of 61.7 min and avoids surgical

interruption^[23], delivering viable near-real-time intraoperative guidance potential.

4.4 Study Limitations

Several inherent limitations exist within this research:

1. Formalin-fixed cadaver specimens cannot replicate in vivo physiological dynamics including blood flow, cerebrospinal fluid circulation, intraoperative hemorrhage and vasogenic edema.

2. Formalin fixation may alter native acoustic and mechanical properties of living brain tissue.

3. Common clinical deformation triggers such as intraoperative brain retraction and cyst fluid aspiration were excluded from the experimental design.

4. TRE measurement accumulates noise from multiple repeated coordinate re-registration steps, making independent quantification of each error source impossible.

5. All image annotation was completed by a single radiologist; multi-observer joint labeling will be adopted in subsequent research to mitigate subjective bias.

5. Conclusions

This study verified the feasibility of 3D intraoperative ultrasound-driven deformation field computation for virtual MRI synthesis to compensate intraoperative brain shift via in vitro phantom and intact human cadaver models. The corrected registration accuracy reached clinically acceptable thresholds (2.94 mm for phantoms, 2.28 mm), offering a low-cost intraoperative navigation alternative for medical centers without iMRI equipment. Future research directions include integrating contrast-enhanced ultrasound (CEUS), shear wave elastography (SWE) and superb microvascular imaging (SMI) to construct multi-constraint deformation models^[24-27] and enhance algorithm robustness under complex acoustic environments; developing deep learning fast registration architectures to reduce runtime from minutes to seconds; conducting prospective in vivo clinical trials to evaluate real-world surgical performance; establishing standardized intraoperative 3D ultrasound acquisition and quality control protocols.

Statements and Declarations

Funding: This research was funded by the Guangzhou Science and Technology Plan Project, Grant No. 2023A03J0728.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions: Conceptualization: L.W., C.L., X.W.; Methodology: X.W., X.Z., R.H.; Software: X.Z.; Validation: X.W., X.Z., R.H., C.H., Y.O.; Formal Analysis: X.W., X.Z.; Investigation: L.W., C.L., J.W.; Resources: L.W., C.L., J.W.; Data Curation: X.W., X.Z.; Writing – Original Draft: X.W.; Writing – Review & Editing: L.W., C.L., X.Z., R.H., C.H., Y.O., J.W.; Visualization: X.W., X.Z.; Supervision: L.W., C.L., J.W.; Project Administration: L.W., C.L., J.W. All authors read and approved the final manuscript.

Data Availability: The raw phantom and cadaver multimodal imaging datasets generated in this study are available from the corresponding author upon reasonable request.

Ethics Approval: The cadaver specimens used in this study were obtained from the body donation program of Sun Yat-sen University. This study was exempted from ethical review by the Institutional Review Board of The Third Affiliated Hospital, Sun Yat-sen University.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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